REMARKS

This Reply is responsive to the Office Action dated May 23, 2003. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 are respectfully requested.

Claims 8-20 were pending in this application at the time of the Office Action dated May 23, 2003. Claims 14-20 were withdrawn from consideration. As a result of this amendment, claims 9, 11 and 13-20 have been canceled. Accordingly, claims 8, 10 and 12 are now pending and under examination.

Applicants acknowledge with appreciation the Examiner's decision to rejoin Groups 5 and 6, defined in the restriction requirement as being drawn to fragments corresponding to SEQ ID Nos. 5 and 6, respectively. Claims 8, 10 and 12 were amended above to limit the subject matter of the claims to the elected subject matter of fragments of the PIR domain of the protein hGrb14 corresponding to SEQ ID Nos. 5 and 6. No prohibited new matter has been added.

According to the Office Action, Figures 4-7 were objected to for failing to contain appropriate labels on their X and Y axes. Corrected drawings are attached hereto. Therefore, the drawings objection may be withdrawn. Applicants note that a Form PTO-948 from the Official Draftsman has not been received. Accordingly, Applicants respectfully request review of all figures by the Official Draftsman at this time.

Claim 9 was objected to for being drawn to a non-elected invention. Claim 9 has been canceled as indicated above, therefore, the objection may be withdrawn. Applicants note that a Form PTO-948 from the Official Draftsman has not been received.

Accordingly, Applicants respectfully request review of all figures by the Official Draftsman at this time.

Claims 10-13 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being admittedly enabled for an in vitro method of detecting molecules capable of modulating the tyrosine kinase activity of the insulin receptor wherein the PIR domain or the PIR-SH domain is SEQ ID No. 5 or SEQ ID No. 6, allegedly fails to enable an in vivo method using any PIR domain. Without necessarily agreeing with the rejection, Applicants note that claims 10 and 12 have been limited to in vitro methods by way of amendment above, and claims 11 and 13 have been canceled. In this regard, Applicants believe that it was unreasonable to read claim 10 as being inclusive of *in vivo* detection in view of the specification. Accordingly, addition of the phrase "*in vitro*" is not a narrowing amendment. In any case, the rejection under 35 U.S.C. §112, first paragraph, may be withdrawn.

Claim 10 was rejected under 35 U.S.C. §103(a) as being unpatentable over Kasus-Jacobi et al. in view of Dunnington et al. (US 5,840,536) and O'Neill et al. According to the Office Action, Kasus-Jacobi allegedly teaches a method of bringing an activated insulin receptor into contact with Grb14's PIR or PIR-SH domains, adding a tyrosine kinase substrate and measuring tyrosine kinase activity. Although Kasus-Jacobi admittedly does not teach adding a test molecule to be tested for its modulating ability, the Examiner believes that this would have been an obvious modification in view of the GrbIR-1 assay taught by Dunnington et al., given that GrbIR-1 is a member of the Grb7

protein family as allegedly taught by O'Neill et al. Applicants respectfully traverse the rejection.

At the outset, Applicants note that claim 10 has been amended as indicated above to refer to the use of PIR fragments of hGrb14 corresponding to SEQ ID Nos 5 and 6. Kasus-Jacobi et al. teach that the fragments PIR, SH2 and PIR-SH2 of rGrb14 interact with the receptor of insulin. However, the reference states that, although rGrb14 binds to activated insulin receptors, it is not a substrate of tyrosine kinase (see page 26032, right column). Further, while the reference defines a region of protein-protein interaction involving the PIR domain in rGrb14 and the phosphorylated insulin receptor (page 26033, left column), it indicates that the function of rGrb14 binding is still not known (see page 26034, right column). For instance, the reference postulates that "rGrb14 could either inhibit tyrosine kinase activity by masking access to the catalytic site, or it could maintain the enzyme in an active conformation by stabilizing the phosphorylated loop," indicating that further studies are needed. Thus, there is nothing in Kasus-Jacobi et al. to suggest that PIR fragments may be used in an assay such as that recited in claim 10 to detect molecules capable of modulating the tyrosine kinase activity of the receptor.

The Office Action asserts that the motivation for detecting molecules capable of modulating tyrosine kinase activity using PIR fragments of proteins from the Grb7 family of proteins could be gleaned from Dunnington et al., which allegedly teaches an assay for detecting a molecule which modulates the function of GrbIR-1, the human homolog of Grb10 as taught by O'Neill et al. However, there is nothing in the disclosure of Dunnington et al. or O'Neill et al. to suggest that such an assay could be performed with

a fragment from the PIR domain. Further, one would not be motivated to combine the disclosure of Dunnington et al., which concerns the Grb10 protein, with the disclosure of Kasus-Jacobi et al., which concerns the rGrb14 protein, since Kasus-Jacobi et al. clearly states that rGrb14 is not tyrosine phosphorylated while Grb10 is susceptible to tyrosine phospharylation (see page 26032, right column). Kasus-Jacobi et al. also discloses that the SH2 domains of the two proteins "play different functions in association with the insulin receptors" (page 26033, right column). In fact, Kasus-Jacobi note that both the PIR domain and the SH2 domain of Grb10 are necessary for inhibiting the activity of the insulin-like growth factor-1 receptor.

Thus, Kasus-Jacobi et al. would not motivate the skilled artisan to use exclusively fragments of the PIR domain with the receptor of activated insulin in a method of screening for molecules that modulate tyrosine kinase activity of the receptor, since the document does not suggest that the PIR domain presents a direct inhibitory activity on the tyrosine kinase activity of the receptor. Moreover, since it is clearly disclosed in Kasus-Jacobi et al. that different proteins of the Grb7 family, i.e., rGrb14 and Grb10, do not possess the same properties, the skilled artisan has no reason to combine or extrapolate the results obtained with rGrb14 in Kasus-Jacobi et al. or GrbIR-1/Grb10 in Dunnington et al. to any other protein of the Grb7 family. The Examiner's comments in paragraph 10 of the Office Action agree in this regard. Thus, the cited references neither teach nor render obvious the unexpected results of the present invention, i.e., that the PIR domain alone has activity as an inhibitor of the tyrosine kinase of the insulin receptor, nor that in

light of this activity effective assays for identifying molecules capable of modulating the insulin receptor tyrosine kinase activity be developed.

In support of the arguments above, Applicants submit herewith a declaration under 37 CFR §1.132 by Anne-Françoise Burnol, who is a coinventor of the present invention and a coauthor of Kasus-Jacobi et al. Applicants note the lack of clarity in the document communicated by facsimile and will provide a legible copy of the declaration or the original declaration per se upon receipt. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) in view of the remarks above and the declaration of Dr. Burnol are respectfully requested.

Applicants note with appreciation that claims 8 and 12 were found to be free of the prior art. This reply is fully responsive to the Office Action dated May 23, 2003. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, he[she] is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,

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